backbone plasmids are made. Artisans in the molecular biology arts are recognized as having a high level of skill. Applicant asserts that the named backbone plasmids are adequately described in the specification so that one of ordinary skill in the art in possession of the present specification could readily make the backbones. It would only require simple cloning in order to generate the backbones, once an artisan is instructed which portions of the Ad genome to use or modify. The specification need not teach, and preferably omits, what is well known in the art to satisfy the enablement requirement. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986).

As is customary in the art, the designation "pac" in the name of the backbone plasmids stands for PacI, which is a restriction enzyme site that flanks the sequences in the various named Ad9.2-100 plasmids recited in the claims.

It should be noted that the backbone plasmids listed in the pending claims do not include lox P sequences.

35 U.S.C. §112 Rejection of the Claims

The final Office Action mailed June 18, 2002 and the Advisory Action dated October 21, 2002 maintained that the pending claims where indefinite under 35 U.S.C. § 112, second paragraph for reciting "comprising essentially of" and "lacks a loxP sequence." All previously pending claims have been cancelled, thereby rendering this rejection moot. Applicant therefore requests that the Examiner withdraw the rejection under 35 U.S.C. § 112, second paragraph.

35 U.S.C. §103 Rejection of the Claims

1. Aoki et al. in view of Chinnadurai et al.

Claims 4, 5, 10, 11 and 13-25 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Aoki *et al.* (Molecular Medicine, 5: 224-231 (1999)) and Chinnadurai *et al.* (Journal of Virology, 32(2): 623-628 (1979)). All of these claims have been cancelled, thereby rendering this rejection moot. Insofar as the Examiner may apply this rejection over the pending claims, Applicant presents the following statements.

In order to establish a *prima facie* cases of obviousness, all three of the following factors must be met. First, the references themselves must teach or suggest all the limitations of the claims. Second, there must be a reasonable expectation of success at the time the invention was made. Third, the prior art must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference, or to combine references.

Chinnadurai *et al.* teach growing Ad2 and Ad5 viral particles, protein digesting the particles, isolating the full-length genomes from the viral particles, digesting Ad2 DNA with *Eco*RI and Ad5 with *Sal*I, and then co-transfecting the digested DNA into 293 cells. Chinnadurai *et al.* found that recombination occurred between Ad2 *Eco*RI-A (map position 0 to 59) and Ad4 *Sal*I-A (map position 45 to 100). Chinnadurai *et al.*, Introduction, p. 623. The recombination seen by Chinnadurai *et al.* was between map positions 45 to 59.

The Ad plasmids (and methods) of the present claims differ from the DNA used by Chinnadurai *et al.* in their recombination experiments. Chinnadurai *et al.* do not teach a recombinant adenovirus used in the pending claims. Further, Chinnadurai et al. do not teach the use of plasmids at all; they only teach full-length infectious viral DNAs. Moreover, they do not teach a one-step transfection method. Therefore, Chinnadurai *et al.* alone does not anticipate the pending claims.

Aoki *et al.* do not teach the method of the pending claims. Page 225 of the reference describes the method used by Aoki *et al.* to generate their recombinant virus. Their method involved four steps: (1) in a cell-free reaction mixture equal moles of shuttle plasmid and adenoviral cosmid were recombined *in vitro* for 3 hours at 37°C along with Cre recombinase (except in the negative control), (2) the reaction mixture was inactivated at 70°C for 5 minutes, (3) DNA was purified using a plasmid purification kit, and (4) the DNA was transfected into 293 cells. In contrast, the method of the pending claims is a simple one-step process where a host cell is contacted with a shuttle plasmid and a backbone. No additional *ex vivo* enzymatic recombination, enzymatic inactivation, or DNA purification steps are required in the present method. Therefore, Aoki *et al.* alone does not anticipate the present one-step method claims.

Further, Aoki *et al.* does not teach the backbone plasmids or shuttle plasmids as recited in the pending claims 29-34. The Aoki *et al.* plasmids contain loxP sequences (even in the negative control), whereas the claimed plasmids do not. Therefore, Aoki *et al.* alone does not anticipate the pending claims.

Applicant asserts that even if Aoki *et al.* is combined with Chinnadurai *et al.*, these references do not teach the present invention. Neither Aoki *et al.* nor Chinnadurai *et al.* teach or suggest the backbone plasmids or shuttle plasmids as recited in the pending claims 29-34. Therefore, Chinnadurai *et al.* in combination with Aoki *et al.* do not teach the invention recited in claims 29-34.

Further, neither Aoki *et al.* nor Chinnadurai *et al.* teach or suggest the invention of claims 27-28. When finding a claimed invention obvious, the references relied on must be considered as a whole, and must also suggest the desirability of making the combination. *Lindemann Maschinefabrik GmbH v. American Hoist and Derrick Co.*, 221 USPQ 481, 488 (Fed. Cir. 1984). Furthermore, "[w]e do not 'pick and choose among the individual elements of assorted prior art references to recreate the claimed invention' but rather, we look for 'some teaching or suggestion in the references to support their use in the particular claimed combination.'" *Symbol Tech., Inc. v. Opticon, Inc.*, 19 USPQ2d 1241, 1246 (Fed. Cir. 1991) (quoting *Smithkline Diagnostics, Inc. v. Helena Lab. Corp.*, 8 USPQ2d 1468, 1475 (Fed. Cir. 1988)); *see also, In re Sang Su Lee*, 61 U.S.P.Q.2d 1430-1436, 1433 (Fed. Cir. 2002).

The prior art does not contain some suggestion or incentive that would have motivated the skilled artisan to modify or to combine these references. The Introduction section of Aoki *et al.* discusses homologous recombination in mammalian helper cells between shuttle plasmid and an overlapping DNA of virus origin that has been rendered noninfectious. Aoki *et al.* specifically cites to Chinnadurai *et al.* regarding this homologous recombination method. Aoki *et al.* continues, however, by stating, "since homologous recombination is a rare event in mammalian cells, these procedures are often unpredictable, time-consuming, and difficult to control. To circumvent these problems of efficiency and contamination of wild-type adenovirus, we proposed using Cre-loxP recombination *in vitro*." Aoki at p. 224-225. Thus, one of ordinary

skill in the art would not have had a reasonable expectation of success at the time the invention was made because there were so many known problems associated with homologous recombination methods.

Oftentimes one must guess at what one of ordinary skill in the art would do given the knowledge of the time. Here, we have the luxury of specifically knowing what one of skill in the art who was specifically aware of the teachings of Chinnadurai *et al.* and obviously the teachings of Aoki *et al.* (their own work). Aoki *et al.* were definitely skilled in the art and were aware of Chinnadurai *et al.*, and they chose to develop the Cre-loxP system, and not the system of the present invention. Thus, Aoki *et al.* taught away from using homologous recombination methods, and instead taught enzymatic recombination.

Further, Aoki *et al.* and Chinnadurai *et al.* cannot logically be combined. Chinnadurai *et al.* teaches a method of performing homologous recombination of infectious viral genomes, so as to generate viral particles. Aoki *et al.* teach a method of performing enzyme-mediated recombination to generate recombinant plasmids. One of skill in the art would not use Aoki *et al.*'s starting materials in the method of Chinnadurai *et al.* because one would not be able to generate the infectious viral genome that was the goal of Chinnadurai *et al.* Thus, the cited references do not contain the requisite suggestion or incentive that would have motivated the skilled artisan to modify a reference, or to combine references.

For these reasons, these references, even when taken in combination, do not meet the three requirements of *prima facie* obviousness. Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 103 be withdrawn.

2. *Aoki et al. in view of Chinnadurai et al. and Krougliak et al.*

Claims 2, 3 and 6 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Aoki *et al.* and Chinnadurai *et al.*, and further in view of Krougliak *et al.* (Human Gene Therapy, 6: 1575-1586 (1995)). These claims are cancelled, thereby rendering this rejection moot.

Insofar as Krougliak *et al.* may be applied to the pending claims, this rejection is hereby traversed. Krougliak *et al.* generated cell lines that could complement E1, E4 and protein IX

defective adenovirus type 5 (Ad5) mutants. The plasmid system used by Krougliak *et al.* contained adenovirus sequences from the left ITR to the right ITR (*i.e.*, the full viral backbone), except for sequences encoding E1, E4 or protein IX. The intention of the deletions by Krougliak *et al.* was to provide for more space to accommodate larger inserts placed into the E1 region of the adenovirus vector and not to otherwise modify the backbone. Both Aoki *et al.* and Krougliak *et al.* devised strategies to make recombinant adenovirus only when the intact recombinant adenovirus genome that contained map units 0-1 and the left ITR was transfected into the cell. Recombination in this region was directly refuted by Aoki *et al.* and not attempted by Krougliak *et al.*, both of whom were extraordinarily skilled in the art.

Thus, none of these references, either alone or taken in combination, teach the present claimed invention. Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 103 be withdrawn.

3. Aoki et al. in view of Chinnadurai et al., Krougliak et al. and Breakfield et al.

Claims 7 and 8 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Aoki *et al.*, Chinnadurai *et al.* and Krougliak *et al.*, and further in view of Breakfield *et al.* (U.S. 5,965,441). These claims are cancelled, thereby rendering this rejection moot.

4. Aoki et al. in view of Chinnadurai et al. and Chartier et al.

Claim 12 was also rejected under 35 U.S.C. § 103(a) as being unpatentable over Aoki *et al.* and Chinnadurai *et al.*, and further in view of Chartier *et al.* (Journal of Virology, 70(7): 4805-4810 (1996)). This claim is cancelled, thereby rendering this rejection moot.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612-373-6961) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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I hereby certify that this paper is being transmitted by facsimile to the U.S. Patent and Trademark Office on the date shown below.

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